Remarks

The Office Action mailed February 17, 2004 has been received and reviewed. Claims 1, 9, and 14-17 having been amended, and claim 5 having been canceled, the pending claims are claims 1-4 and 6-17. Reconsideration and withdrawal of the rejections are respectfully requested.

Interview Summary

A telephonic interview was held on January 20, 2004 between Examiner Nichols, Supervisory Patent Examiner Kunz, and Applicants' Representatives Ann Mueting and Nancy Johnson. Examiners Nichols and Kunz are thanked for the courtesy of this interview.

Double Patenting Rejection

Claims 1-17 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,500,798. Claims 1-17 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-35 of U.S. Patent Application No. 09/641,801. Applicants request that these rejections be held in abeyance. Upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

The 35 U.S.C. §112, First Paragraph, Written Description

The Examiner rejected claims 1-17 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed. Specifically, the Examiner asserted that "claims 1, 9, 14, 15, 16, and 17 recite the limitation 'constituent peptide' while [the] claims do not require that the peptide possess any

particular conserved structure, or other distinguishing feature, such as biological activity" (page 16, Office Action mailed February 17, 2004). In view of the amendment of independent claims 1, 9, and 14-17 to recite "wherein a constituent peptide of colostrinin is selected from the group of SEQ ID NO:1 through SEQ ID NO:34," Applicants submit that the specification provides adequate written description for claim 1-17. Withdrawal of this rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Enablement Rejections

The Examiner rejected claims 1-17 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the claimed methods. Applicants disagree and respectfully traverse this rejection. Applicants submit that the specification provides adequate teaching and guidance for the claimed methods.

As previously presented, with an enablement rejection, "the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, USPQ2d 1510, 1513 (Fed, Cir. 1993). And, "it is incumbent upon the Patent Office . . . to back up assertions of its own with acceptable evidence or reasoning." *In re Marzocchi* 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). "This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. . . . However, specific technical reasons are always required. *In re Marzocchi* 439 F.2d at 224, 169 USPQ at 370 (see also, MPEP 2164.04). Applicants respectfully submit that the Patent Office has failed to meet this burden, has failed to back up its assertions with acceptable evidence or reasoning. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Correlation of PC12 and SH-SY5Y model systems to in vivo results

In rejecting claims 1-17, the Examiner repeatedly asserted that the specification, while being enabling for an *in vitro* method, does not reasonably provide enablement for

practicing said method *in vivo*, in a patient, or using any other cell type (see paragraphs 9, 11, 21, 24, 34, and 37 of the Office Action mailed February 17, 2004). Applicants disagree. First, Applicants respectfully submit that amended claims 1-4 and 6-13 are drawn to pluripotent cells effective to form neuronal cells; claims 14 and 15 are drawn to damaged, nonfunctional neuronal cells; and claims 16 and 17 are drawn to pluripotent cells of the nervous system. Thus, the claims are not drawn to as broad a range of cell types as "any . . . cell type," as the Examiner asserted.

Further, Applicants again submit that the correlation between the *in vitro* model systems provided by the PC12 and SH-SY5Y cells lines and *in vivo* results is well accepted. The Examiner asserted that no evidence, present in the art, the specification, or a declaration "would lead the skilled artisan to this conclusion" (paragraph 11, page 5 of Office Action mailed February 17, 2004). Applicants disagree and, again, refer the Examiner to the following representative sampling of the scientific literature, supporting the correlation between *in vitro* results with the SH-SY57 and PC12 cells lines and *in vivo* results:

Noble et al., *Molecular Pharmacology*, 2000;58:159-166; Demonstrating the similarity of the stimulation of μ- or δ-opioid receptors both *in vitro* in the SH-SY57 cell line and *in vivo* in different strains of mice and rats.

DeJongh et al., *Toxicology and Applied Pharmacology*, 1999; 158:261-268; Demonstrating acrylamide toxicity both *in vitro* in the SH-SY5Y cell line and *in vivo* in rats.

Chen et al., *Journal of Neurochemistry*, 1998;70(4): 1768-1771; Demonstrating the induction of tyrosine hydroxylase by lithium both *in vitro* in the SH-SY5Y cell line and *in vivo* in the frontal cortex, hippocampus, and striatum of male Wistar rats.

Ponthan et al., *Int. J. Cancer*, 2003;104: 418-424; Demonstrating toxicity and antiproliferative effects of the synthetic retinoid Ro 13-6307 both *in vitro* in SH-SY5Y cells and *in vivo*, in a rat neuroblastoma xenograft model.

Zhen et al., *Psychopharmacology*, 2002;162: 379-384; Demonstrating the stimulation of protein tyrosine phosphatase (PTPase) by lithium both *in vitro* in the PC12 cell line and *in vivo* in rat brains.

Dago et al., *Journal of Neurochemistry*, 2002;81: 17-24; Demonstrating the correlation of the neuroprotective effect of compound NS1231 *in vitro* in PC12 cells with the neuroprotective effect of compound NS1231 *in vivo* in both a gerbil model of transient global ischaemia and a mouse middle cerebral artery occlusion model.

Bagchi et al., *Toxicology Letters*, 1997;91: 31-37; Demonstrating similar protein kinase C (PKC) stimulatory effects *in vitro*, with the PC12 cell line, and *in vivo*, with Sprague-Dawley rats, by the administration of various pesticides and transition metal salts, all known to induce oxidative stress.

Applicants provide the above citations to Noble et al., DeJongh et al., Chen et al., Ponthan et al., Zhen et al., Dago et al., and Bagchi et al. as evidence that the correlation between *in vitro* results obtained with the SH-SY57 and PC12 cells lines and *in vivo* results is well accepted. However, the Examiner asserted that the information included in these references "has not been considered," as the references "fail to comply with 37 CFR 1.98 (a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office" on an Information Disclosure Statement" ("IDS") (paragraphs 11 and 27, Office Action mailed February 17, 2004). The Examiner is incorrect in this assertion. The Noble et al., DeJongh et al., Chen et al., Ponthan et al., Zhen et al., Dago et al., and Bagchi et al. references were listed on an IDS submitted to the U.S. Patent and Trademark Office on July 18, 2003. Copies of all of these references were included with the IDS. Further, the Examiner has included an initialed copy of this IDS (with the Noble et al., DeJongh et al., Chen et al., Ponthan et al., Zhen et al., Dago et al., and Bagchi et al. citations initialed as considered by the Examiner) with the most recent Office Action (mailed February 17, 2004) and the Office Action mailed August 15, 2003. Applicants submit that the Examiner has received copies of the Noble et al., DeJongh et al.,

Chen et al., Ponthan et al., Zhen et al., Dago et al., and Bagchi et al. documents in proper format for consideration.

Applicants submit, as supported by Noble et al., DeJongh et al., Chen et al., Ponthan et al., Zhen et al., Dago et al., and Bagchi et al., the correlation between the *in vitro* model systems provided by the PC12 and SH-SY5Y cells lines and *in vivo* results is well established. Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is requested.

Immunomodulatory effects of colostrinin

To support the rejection of claims 1-17, the Examiner cited various references discussing the immunomodulatory activities of colostrinin, including Popik et al., Inglot et al., WO 98/14773, Kruzel et al., and Zimecki et al. (see paragraphs 15, 23, 31, 38, 41, and 42 of the Office Action mailed February 17, 2004). From these teachings the Examiner concluded that, as the prior art is silent on any neuronal cell regulator properties of colostrinin, the skilled artisan would doubt that colostrinin analogs act as neuronal cell regulators and change cell morphology.

Applicants agree with the Examiner that the prior art is silent on any neuronal cell regulator properties of colostrinin. However, Applicants submit, as previously presented in responses to office actions submitted on January 7, 2003, July 18, 2003, November 17, 2003, and December 15, 2003, that the Applicants' specification provides adequate guidance to allow the skilled artisan to practice the claimed methods.

The Examiner has rejected claims 1-3, 6, 7, 9, 11, 12, 14, 15, 16, and 17 as being anticipated by Janusz et al. (*Molecular Immunology*, 1987;24(10): 1029-1031) and claims 1-4, 6, 9, 10, 11, 12, 14, 15, 16, and 17 under 35 U.S.C. §102 as being anticipated by Inglot et al. (*Archivum Immun et Thera Exper*, 1996;44(4): 215-224). Both Janusz et al. (*Molecular Immunology*, 1987;24(10): 1029-1031) and Inglot et al. (*Archivum Immun et Thera Exper*, 1996;44(4): 215-224) teach the immunomodulatory activities of orally administered colostrinin. "To anticipate, the reference must also enable one of skill in the art to make and use the claimed

invention." *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed Cir. 1985). Thus, Applicants are puzzled by the Examiner's use of teachings of the immunomodulatory activities of colostrinin to support a lack of enablement rejection of the claimed methods while at the same time rejecting the claimed methods as anticipated by teachings of the immunomodulatory activities of colostrinin. Applicants submit that the specification provides sufficient knowledge and guidance to enable the claimed methods. Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is requested.

In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejection

The Examiner rejected claims 1-3, 6, 7, 9, 11, 12, 14, 15, 16, 17 under 35 U.S.C. §102(b) as being anticipated by Janusz et al. (*Molecular Immunology*, 1987;24(10): 1029-1031). The Examiner also rejected claims 1-4, 6, 9, 10, 11, 12, 14, 15, 16, and 17 under 35 U.S.C. §102(b) as being anticipated by Inglot et al. (*Archivum Immun et Thera Exper*, 1996;44(4): 215-224). These rejections are respectfully traversed.

The Examiner asserted that Janusz et al. teaches the administration of a constituent peptide of colostrinin, an active analog thereof, and SEQ ID NO:31 to mice and, thus, anticipates claims 1-3, 6, 7, 9, 11, 12, and 14-17 (paragraph 52, page 19 of Office Action mailed February 17, 2004). The Examiner also asserted that Inglot et al. teaches the oral administration of colostrinin, a constituent peptide thereof, and an active analog thereof to humans and, thus, anticipates claims 1-4, 6, 9-11, and 14-17 (paragraph 58, page 19 of Office Action mailed February 17, 2004). Applicants submit that "[t]o anticipate, the reference must also enable one of skill in the art to make and use the claimed invention." *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed Cir. 1985). And, the reference must describe the claimed invention, including all claim limitations, with "sufficient clarity and detail to establish

that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375, 62 U.S.P.Q.2d (BNA) 1917, 1921 (Fed. Cir. 2002).

Thus, in view of these rejections of the claimed methods as anticipated by Janusz et al. and Inglot et al., Applicants insist that the Examiner withdraw his rejection of claims 1-17 under U.S.C. §112, first paragraph, based on his assertions that the specification does not reasonably provide enablement for practicing the claimed methods.

With these rejections, the Examiner further asserted that the "claims are drawn to a method which comprises the step of contacting cells with a 'neuronal regulator'" and that "[n]o other limitations are present in the claims" (paragraph 51, page 19 and paragraph 57, page 20 of Office Action mailed February 17, 2004). Applicants disagree and submit that the claimed methods include elements in addition to the method step of contacting cells with a neuronal cell regulator. Specifically, claim 1 (and dependent claims 2-4, 6, and 7) is drawn to a "method comprising contacting pluripotent cells effective to form neuronal cells with a neuronal cell regulator . . . under conditions effective to change the pluripotent cells in morphology to form neuronal cells . . . wherein the pluripotent cells change in morphology to form neuronal cells;" claim 9 (and dependent claims 10-12) is drawn to a "method comprising administering to the patient a neuronal cell regulator . . . under conditions effective to promote differentiation of pluripotent cells to form neuronal cells . . . wherein pluripotent cells differentiate to form neuronal cells;" claim 14 is drawn to a "method comprising contacting nonfunctional neuronal cells with a neuronal cell regulator . . . under conditions effective to convert the damaged neuronal cells to functional neuronal cells . . . wherein damaged neuronal cells are converted to functional neuronal cells;" claim 15 is drawn to a "method comprising administering to the patient a neuronal cell regulator . . . under conditions effective to convert damaged neuronal cells to functional neuronal cells . . . wherein damaged neuronal cells are converted to functional neuronal cells;" claim 16 is drawn to a "method comprising contacting pluripotent cells of the nervous system with a neuronal cell regulator . . . under conditions effective to change the

pluripotent cells of the nervous system in morphology to form neuronal cells;" and claim 17 is drawn to a "method comprising administering to the patient a neuronal cell regulator . . . under conditions effective to promote differentiation of pluripotent cells of the nervous system to form neuronal cells . . wherein pluripotent cells of the nervous system differentiate to form neuronal cells." Applicants respectfully submit that neither Inglot et al. nor Janusz et al. teach each and every element of the claimed methods. Withdrawal of the rejections of claims 1-3, 6, 7, 9, 11, 12, 14, 15, 16, 17 under 35 U.S.C. §102 as being anticipated by Janusz et al. and claims 1-4, 6, 9, 10, 11, 12, 14, 15, 16, and 17 under 35 U.S.C. §102 as being anticipated by Inglot et al. is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4 and 6-17 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 201890365 US Date of Deposit: May 17, 2004
The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450.

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